

Severe Pneumonia in Military Personnel Deployed to Southwest Asia

March - August 2003

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Outline

- Background and methods
- Demographic data
- Clinical data
- Risk factors
- Unique features
- Findings to date

Epidemiological Consultation (EPICON)

- Late March 2003: 2 patients in ICU at Landstuhl, Germany
- 17 June 2003: First pneumonia death, reports of additional ICU patients at Landstuhl
- 12 July 2003: Second pneumonia death
- 17 July 2003: Tasking from the OTSG
 - Determine if there was an outbreak of severe pneumonia
 - 3 teams deployed
 - Germany (Landstuhl)
 - Iraq
 - United States

Methodology

- Questionnaire and database development
- Case finding
- Clinician interviews
- Review of charts, radiographs and laboratory tests
- Case interviews (surrogate interviews for the two deaths)
- Autopsy review
- Follow-up clinical evaluations for 13 severe patients at WRAMC
 - Labs, PFTs, PPD, CXR, pulmonary and allergy evaluations
 - Revised questionnaire
- Tobacco analysis

Pneumonia Case Definition

- US military member who served in Southwest Asia from March through August 2003 with the following:
 1. Hospitalized in theater
 2. Chest X-ray suggestive of pneumonia
 3. One or more of these symptoms: fever, cough, SOB
- Severe case = above criteria plus intubation or death

Overall Pneumonia Incidence in SW Asia

Group	Cases	Denominator	Rate *
SWA: March – August 2003	100	135,000 PY	7.4
US Army soldiers [†]	1259	1,428,213 PY	8.8
Army basic training posts [†]	696	188,707 PY	36.9

*Rate per 10,000 person-years

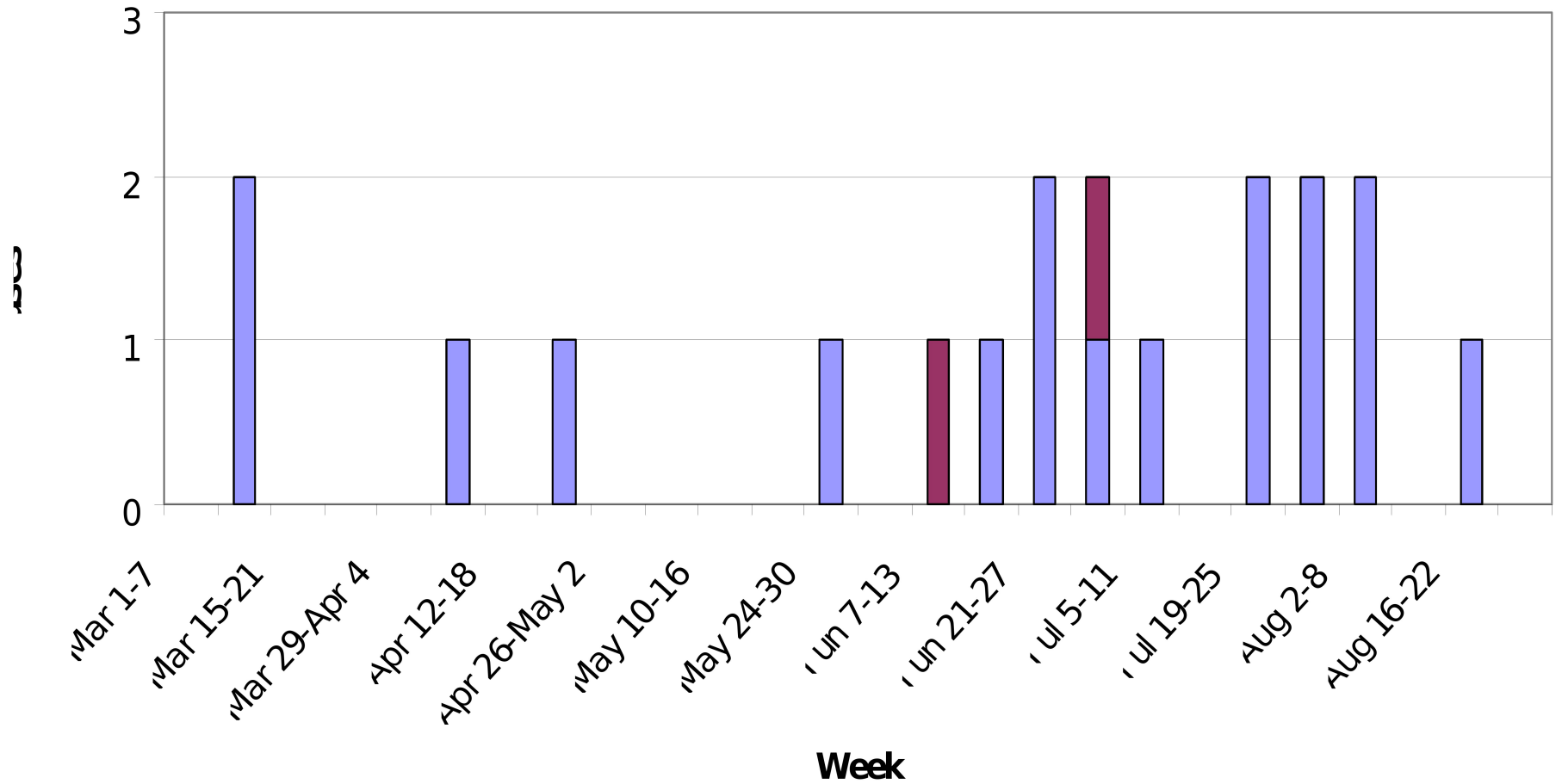
[†]US Army (2000-2002): Calculated by Dr. John Brundage, AMSA

Severe Pneumonia Incidence in SW Asia

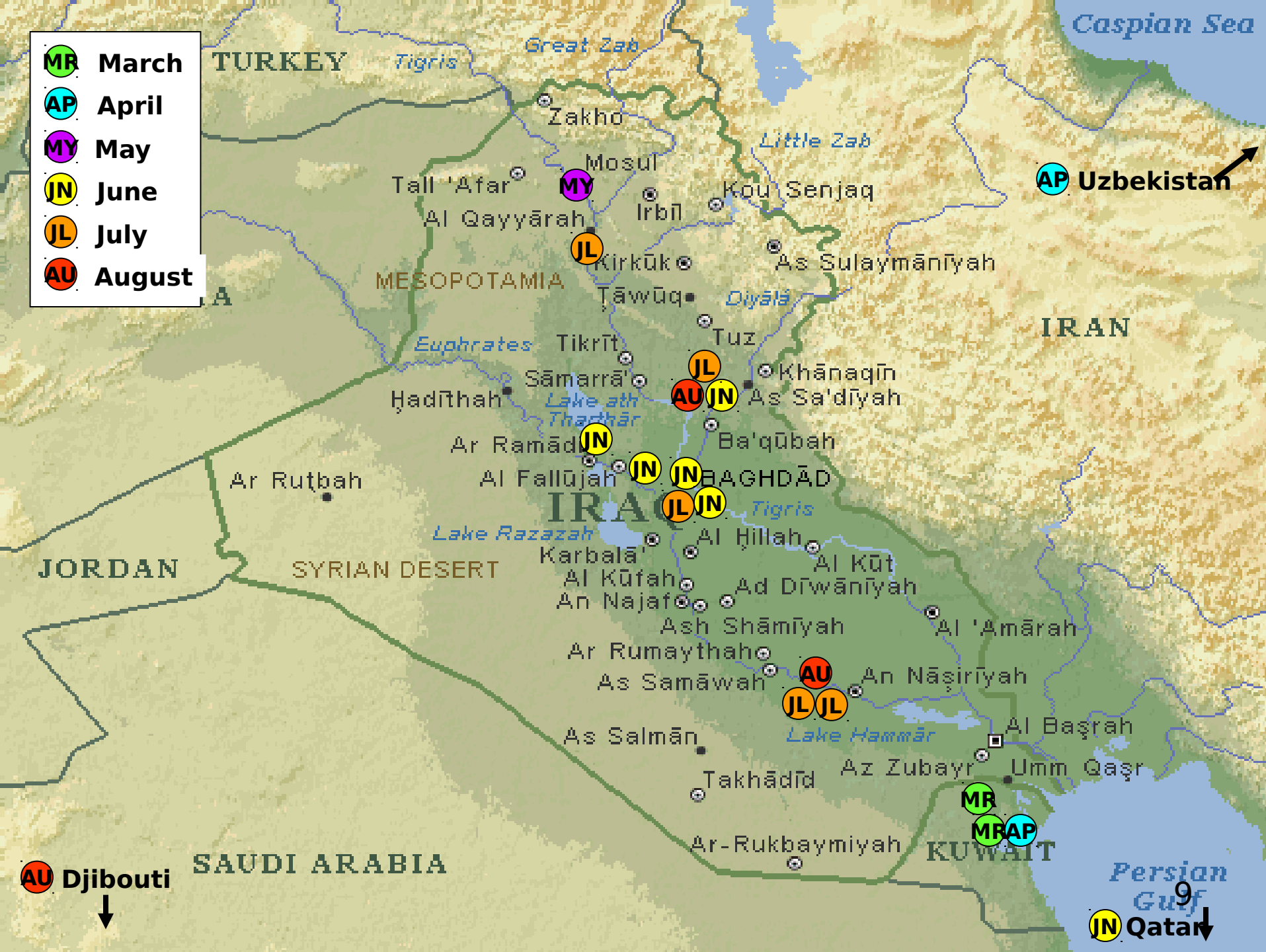
Group	Cases	Denominator	Rate *
SWA: March – August 2003	19	135,000 PY	1.4
Army basic training posts†	4	188,707 PY	0.2

*Rate per 10,000 person-years
 †US Army (2000-2002): Calculated by Dr. John Brundage, AMSA

Severe Pneumonia Cases by Week of Illness Onset



 **Death**



Demographics

Service	N (%)
Army	17 (90)
Navy	1 (5)
Marine Corps	1 (5)
Unit	
C Co 2/8 Infantry, 4 th ID	2* (10)
Other	17 (90)
Evacuation location	
Landstuhl	17 (90)
Rota Fleet Hospital	1 (5)
Not evacuated (death)	1 (5)

**1st case evacuated to Germany before 2nd deployed to Kuwait from the United States; illness separated by 4 months*

SWA Army Cases

3rd PERSCOM

Sex*	N (%)	N (%)
Male	16 (94)	211,794 (88)
Female	1(6)	27,706 (12)
Service Component		
Active	10 (59)	168,496 (70)
Reserve	7 (41)	71,010 (30)
Age* (years)		
Median	24	25
Range	19-40	17-64
Rank*		
≤ E4	10 (59)	122,755 (51)
E5-E9	7 (41)	86,750 (36)
Officer	0	29,721 (12)
Total	17	239,506

*Excludes 6 missing sex; 2,820 missing age; and 280 missing rank

No statistically significant difference between SWA cases and 3rd P

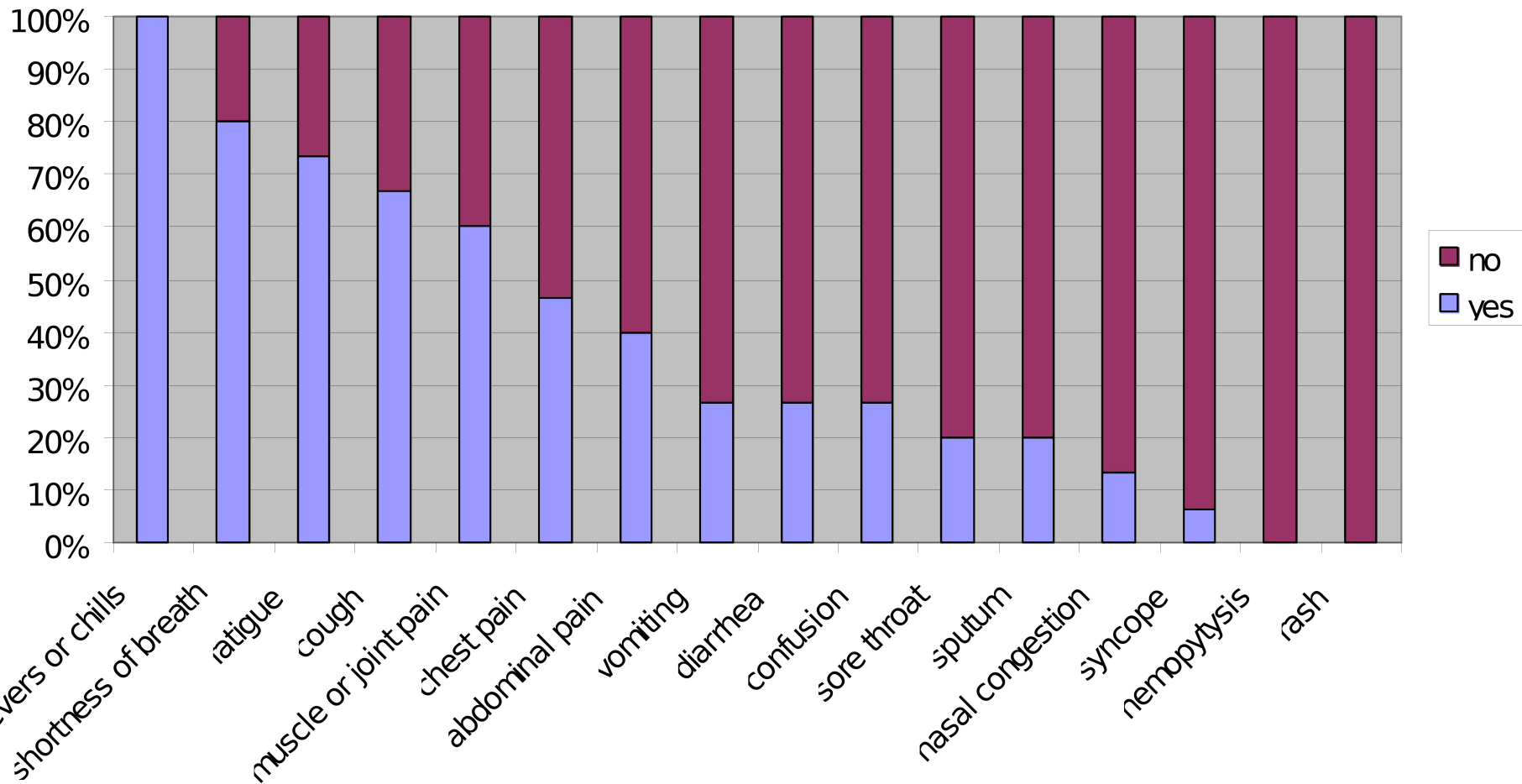
Military Occupation (MOS)

Infantry	3
Armor	2
Artillery	2
Engineer	3
Mechanic	1
Truck driver	2
Fuel/Supply	1
Communication s	3
Medical	2

Medical History

- Generally unremarkable
- No asthma
- Prescription medications
 - Simvastatin (1)
 - Malaria prophylaxis: medication and compliance varied
 - One with latent TB infection; non-compliant with INH
- Over-the-counter medications and supplements
 - Ibuprofen or aspirin as needed (3)
 - Vitamins (3)
 - Creatine (1)
 - OTC stimulant to stay awake (1)

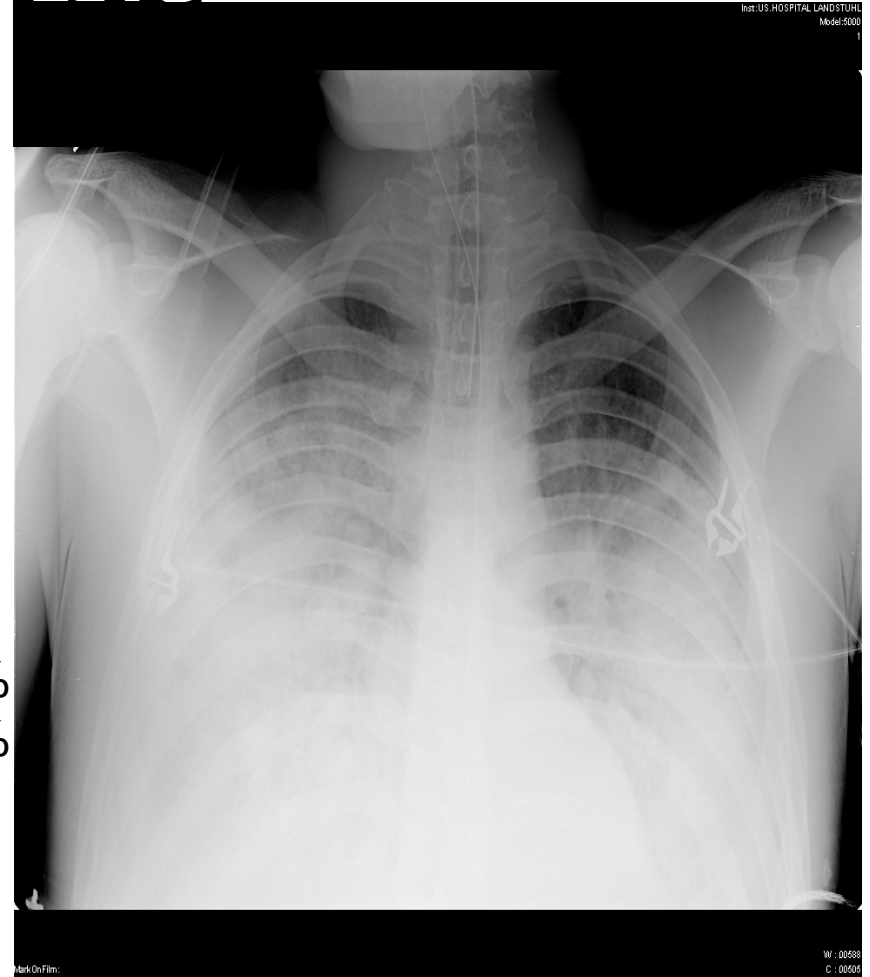
Distribution of Symptoms (n=16)



Overview of Clinical Course

- Symptoms & signs
 - Fever, respiratory distress
 - Elevated WBC count
(Median 13, range 7.3 - 37)
 - CXR w/ bilateral infiltrates
(10 with pleural effusions)
- Antibiotics

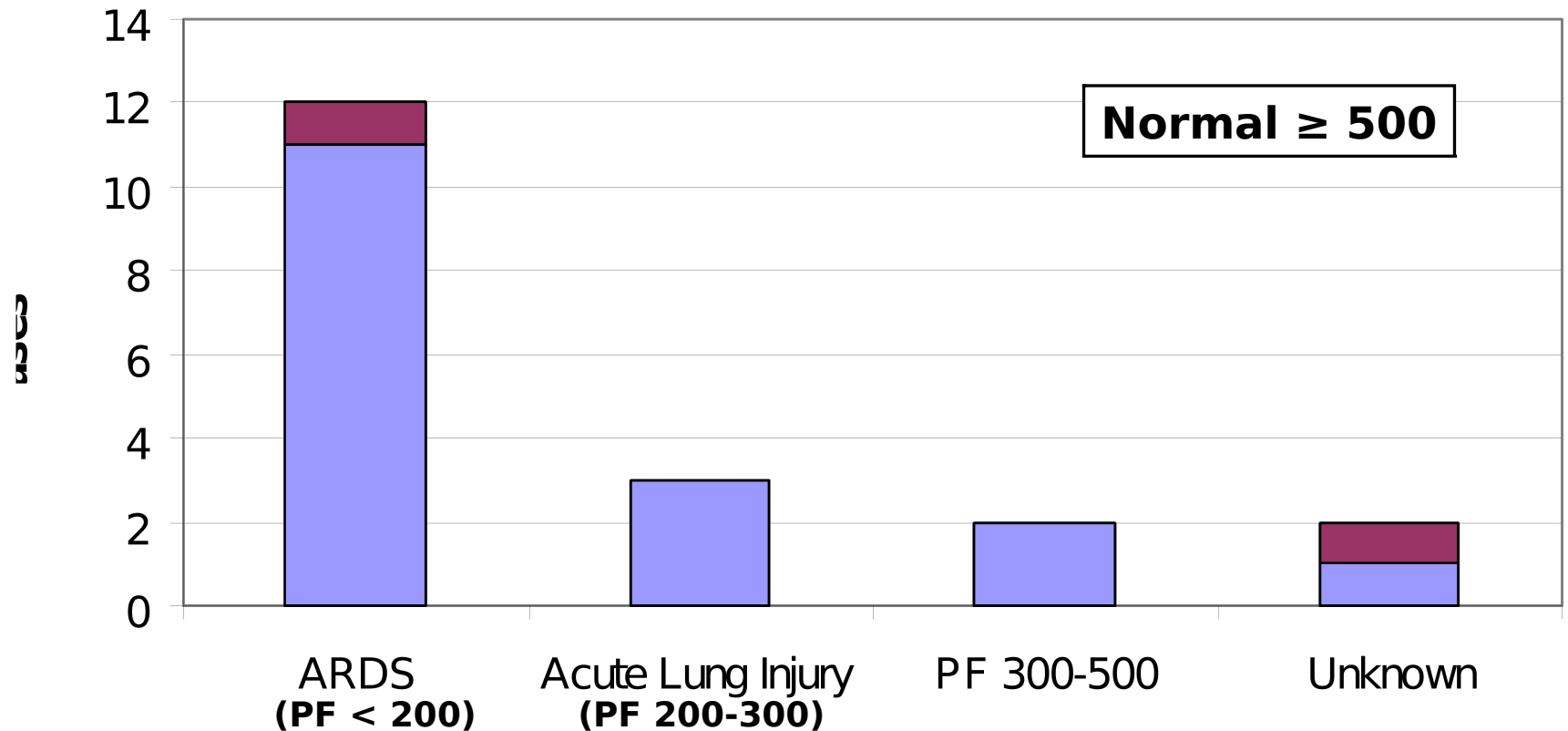
- Levofloxacin	88%	
- Ceftriaxone	65%	
- Doxycycline	59%	
- Imipenem		59%
- Macrolide		47%
- Vancomycin	24%	
- Steroids given to 8 patients



CXR on hospital day #2

Pneumonia Severity (PF Ratio)

Distribution of $\text{PaO}_2 / \text{FIO}_2$



■ Death

Lab Findings

- Culture
 - *Streptococcus pneumoniae* (1) – sputum
 - *Acinetobacter baumannii* (1) – BAL fluid
- Urine antigen
 - *Streptococcus pneumoniae* (1)
- Serology
 - *Coxiella burnetti* (3)
 - *Legionella* spp. (1)
 - Low titers to various respiratory pathogens
 - Fungal & parasitic Abs negative
- Immunology
 - Serum immunoprecipitation to tobacco leaf extracts negative; smoke extracts pending
 - Most patients with evidence of atopy by skin testing

Pneumonia with Elevated Eosinophils

Tissue involvement	4
Lung* ± blood	6
Blood only	
Smoking	
New-onset	8
Chronic	1
Unknown	1
Total	10

*Bronchoscopic alveolar lavage fluid (3)
Pleural fluid (1)
Tissue from autopsy (1)

	Elevated Eosinophils[†]	
	Yes*	No
Non-smoker	0	3
New-onset smoker	8	0
Chronic smoker	1	6

[†]Blood absolute count >600 cells/ μ l; pleural fluid and BAL fluid >5%

*Not in table: 1 patient with elevated eos is a smoker of unknown duration

Time from illness onset to elevated eosinophils
Mean = 7.5 days, median = 6.5 days, range 4-14 days

Pneumonia with Elevated Eosinophils

Drug received	Elevated Eosinophils	
	Yes*	No
Levofloxacin	8	8
Ceftriaxone	4	5
Doxycycline	5	5
Imipenem	6	5
Macrolide	3	5
Vancomycin	3	1
Others	2	4

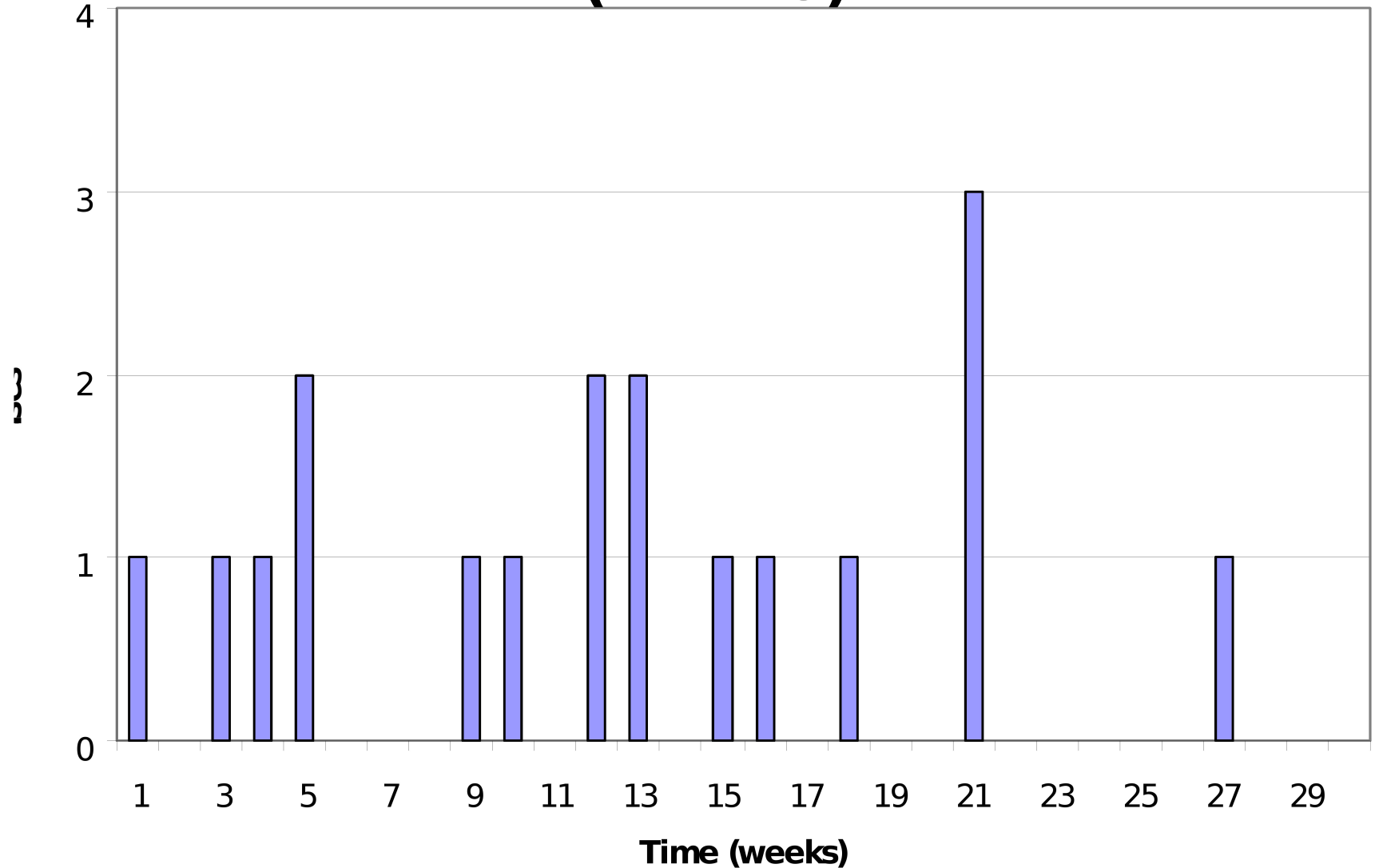
*Lung and/or blood

Questionnaire Results

- No common exposures prior to illness
 - Occupational risk factors (daily duties, chemicals, munitions, fuel, etc)
 - Environmental risk factors (water, food, habitat, pollutants, etc)
 - Infectious risk factors (contact with locals, insects, animals, etc)
 - Medications
- Smoking history
 - 16 smokers
 - 7 smoked both foreign and US tobacco
 - 8 began smoking during this deployment

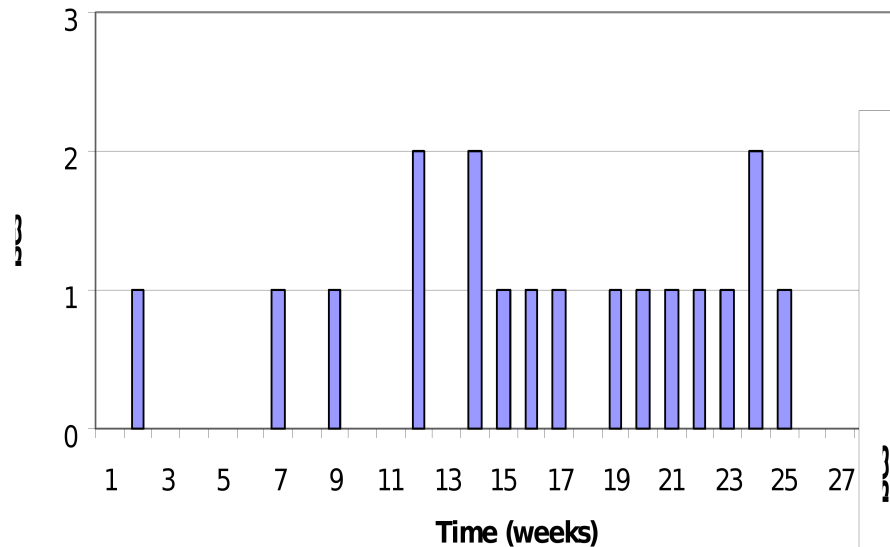
Time from Arrival in Theater to Illness Onset

(n = 18)



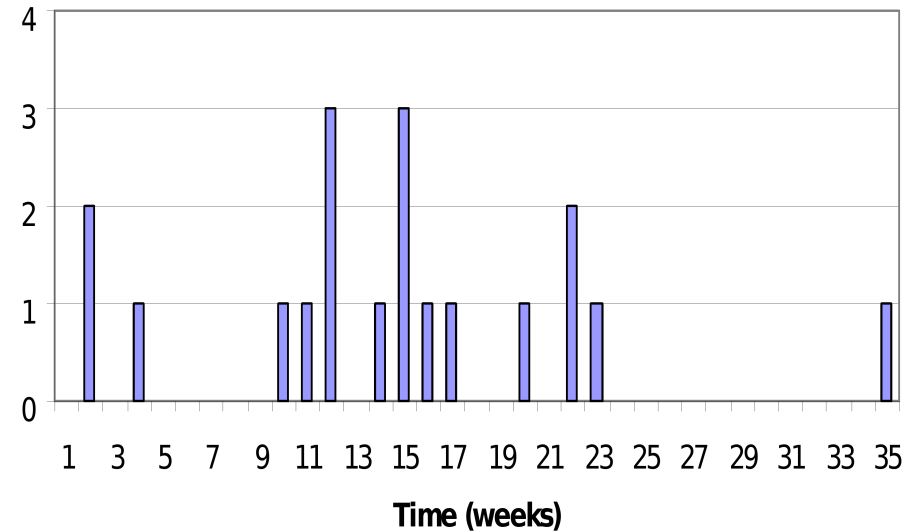
Smallpox* and Anthrax Immunizations

Time Elapsed from Last Smallpox Immunization to Illness



*One patient did not receive smallpox vaccine

Time Elapsed from Last Anthrax Immunization to Illness



Findings to Date

- Higher rate of severe pneumonia compared to Army basic training posts
- Severe pneumonia cases w/o obvious epidemiologic link
 - No relation in person, place or time
 - No common exposures identified
- A variety of possible infectious etiologies for severe pneumonia
- 10 cases with elevated eosinophils
 - New-onset smoking a possible risk factor
 - No common infectious cause, including parasites
 - No specific medication(s) unique to patients with elevated eos
- No evidence of contamination of tobacco products

New Cases

- No pneumonia cases from mid-August 2003 to mid-January 2004
- Two new cases in January 2004
 - Both with rapid onset & severe respiratory distress; one intubated
 - Both with eosinophilia; one had bronchoscopy (BAL fluid w/ 24% eos)
 - Both began smoking during this deployment
 - No infectious etiologies identified to date
 - Complete recovery expected

Ongoing Investigation

- Pneumonia with elevated eosinophils
 - March to August 2003
 - Iraq / Kuwait (11)
 - Djibouti, Uzbekistan, Qatar (1 each)
 - Korea (1)
 - January 2004 (2 from Iraq)
 - Retrospective case finding (1991 to present)
 - 17 other potential cases identified by AMSA
 - NTC (2) in 1997
 - Macedonia (1) in 2000

Ongoing Investigation

- Case-control study of severe pneumonia cases in progress
- Paired serologic analysis of severe cases
- Q-fever serology study
 - Define prevalence and risk in Iraq
 - Could have implications in treatment of pneumonia in Iraq
- Provider education (CENTCOM, LRMC)

Conclusions

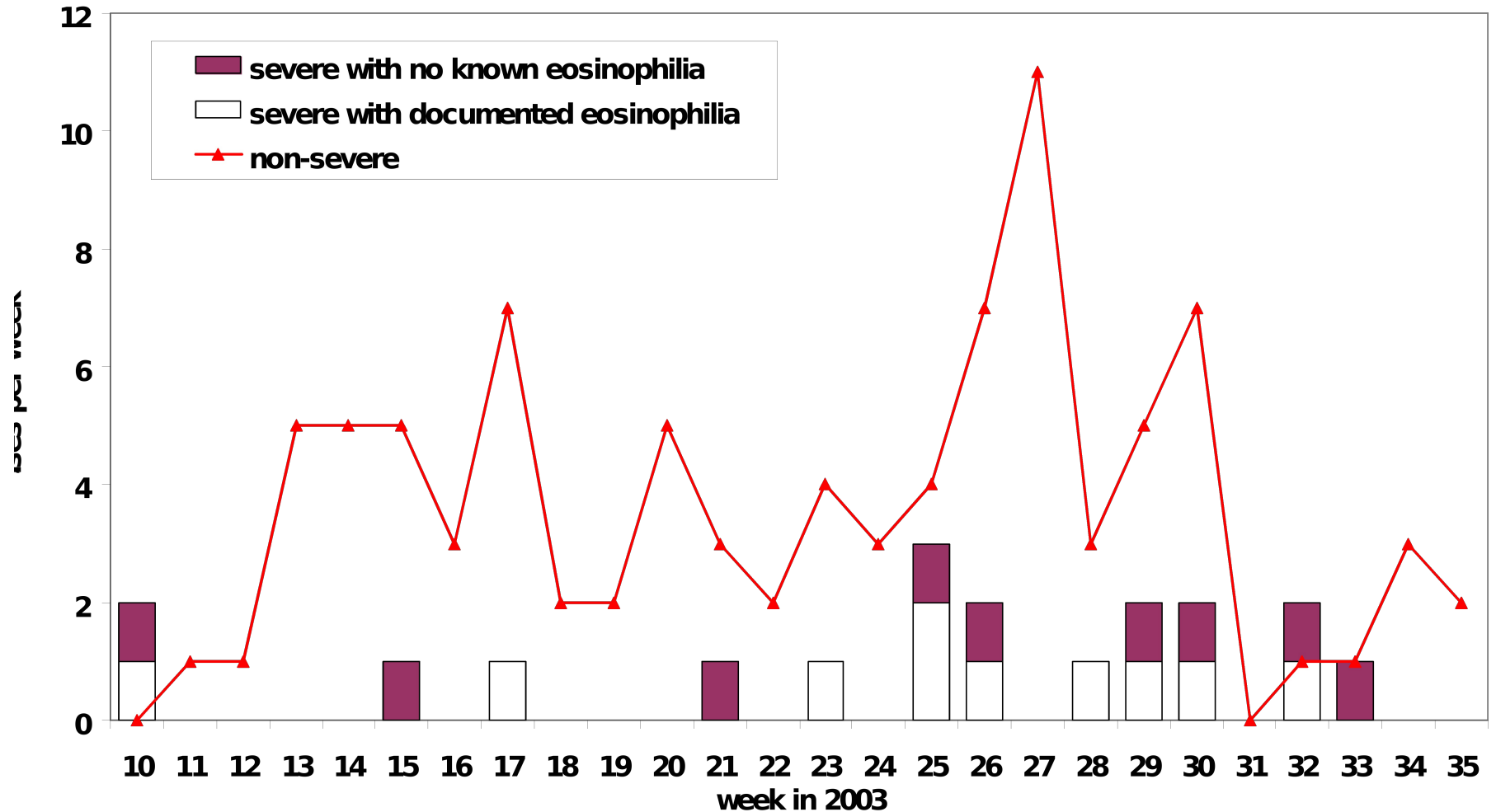
- Multiple potential etiologies
- Individual susceptibility / predisposition
- Stressors
 - Physical (heat, intense activity, lack of sleep, nutritional deficiencies, dehydration)
 - Psychological
- Inhalational insult
 - Dust
 - Tobacco smoke
 - Common infectious agent

EPICON Team Members

- COL Petruccelli
- COL Smoak
- COL Shanks
- COL Ockenhouse
- CAPT Redd
- LTC Shuping
- LTC Pavlin
- CDR Culpepper
- MAJ Cersovsky
- MAJ Shorr
- MAJ Carr
- MAJ Anderson
- MAJ Weg
- CPT Mancuso
- SFC Trainer
- Dr Scoville
- Dr Heller

Questions?

Epidemic Curve



Autopsy Results

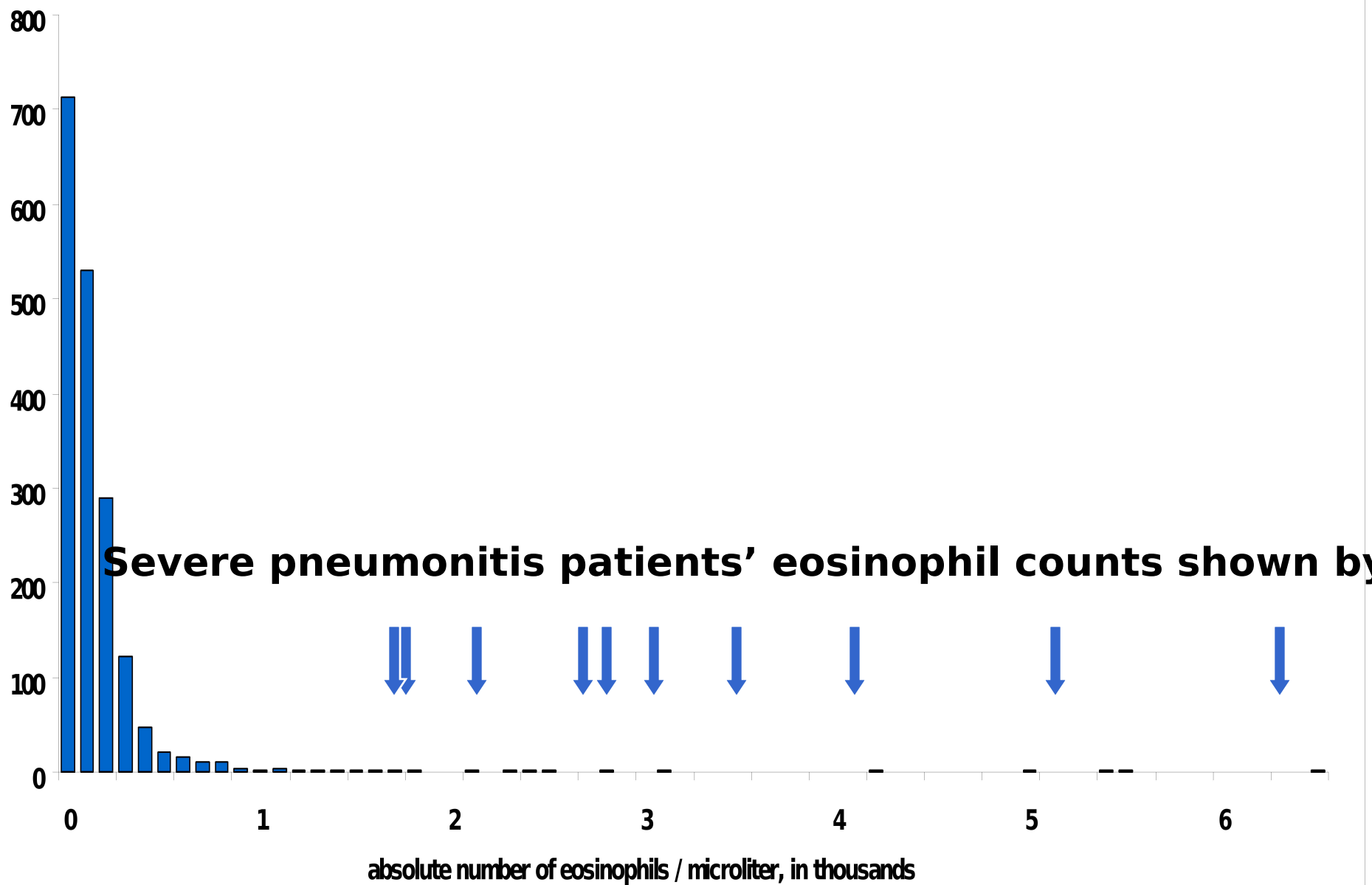
Case 1

Case 2

Time (1st symptoms to death)	6 days	13 days
Cause of death	Diffuse microvascular lung injury	Pneumonia of undetermined etiology with complications*
Lung tissue	Pulmonary edema Diffuse alveolar damage ↑ Eosinophils	Pulmonary edema Diffuse alveolar damage
Microbiology	Negative	<i>Klebsiella pneumoniae</i> ; otherwise negative
Diagnostics	Minimal	Eosinophilia on hospital day 1 32

* *Klebsiella* sepsis was the terminal event, unrelated to primary pulmonary insult, multiple organ system failure

Eosinophil counts from all OIF soldiers with blood drawn at LRMC Mar-Jul 2003

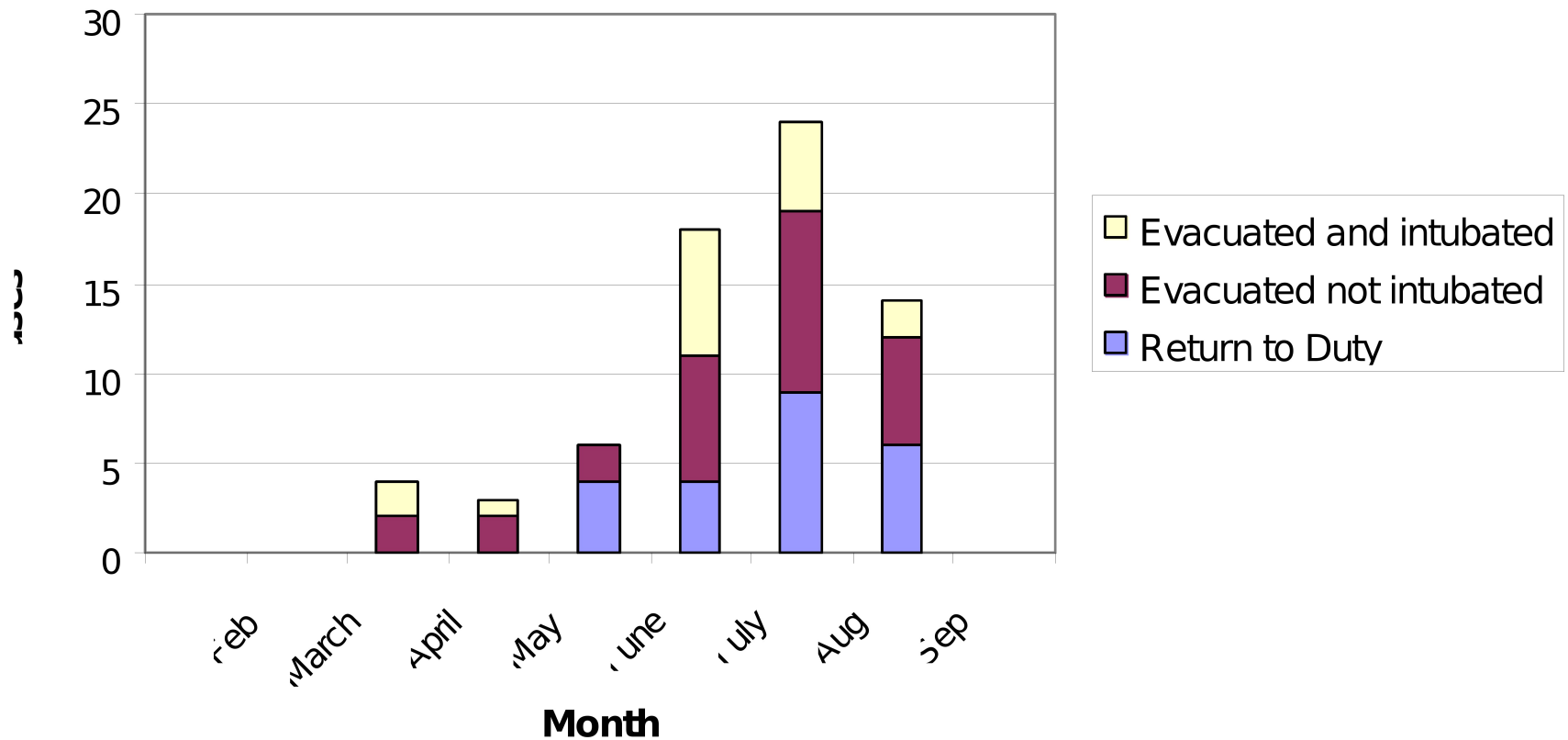


Recommendations

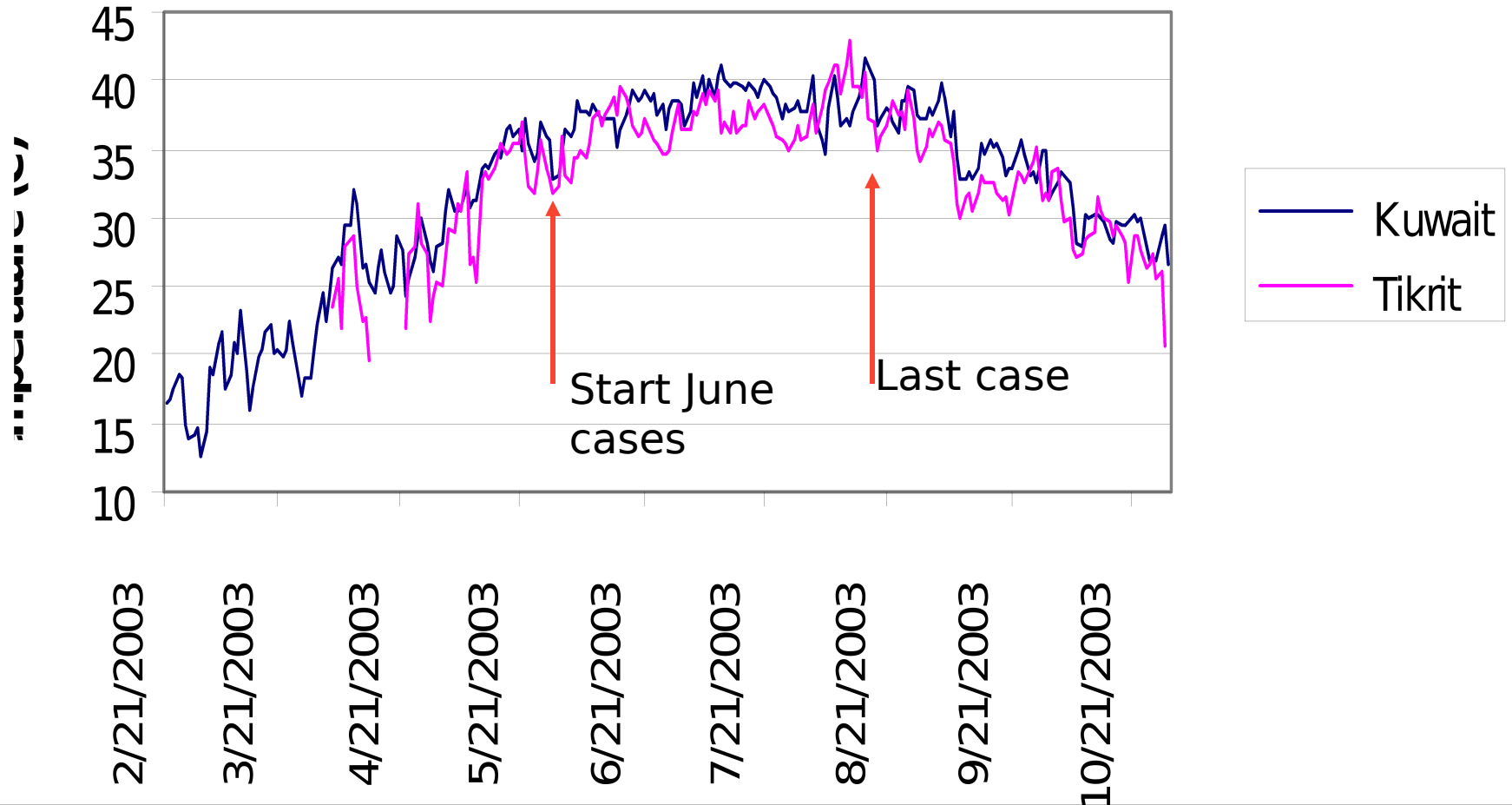
- Microbiologic testing capability in theater
 - *S. pneumoniae*, *Legionella* (urine)
 - Group A streptococcus, Influenza A and B (throat)
- Enhanced operational surveillance
 - Monitor and archive weekly rate of pneumonia admissions
- Standardized diagnostic work-up and treatment (CPG)

Cases by Month (n=69)

Pneumonia Cases by Month



Temperature by Date



Diagnostic Work Up in Theater

- Establish limited diagnostic capabilities for pneumonia
 - Worked with microbiology team to establish limited micro capability at 28th CSH – Baghdad
 - M403 set
 - Training of lab personnel
 - Worked to establish the capability to rapidly diagnose major causes of pneumonia in all Level III facilities with the placement of rapid antigen diagnostic tests for
 - *S. pneumoniae* (urine)
 - Legionella (urine)
 - Group A streptococcus (throat)
 - Influenza A and B (throat)

Treatment Strategies

Uncomplicated

- Oral therapy - Azithromycin (macrolides)
Levofloxacin
- Illness generally resolves in 3-7 days & patients return to duty

Severe

- Require intravenous antibiotic therapy
- Combination therapy directed to specific pathogens
Ceftriaxone (1 gm every 12 hr) - may substitute
Levofloxacin (500 mg every day)
Doxycycline (100 mg every 12 hr)
- Steroids (physician-directed depending upon clinical s
- Air evacuation for definitive diagnostic work-up

Limitations

- Lack of early diagnostic capability
- Incomplete medical records
- Limited information on the two deaths
- Self-report / recall bias

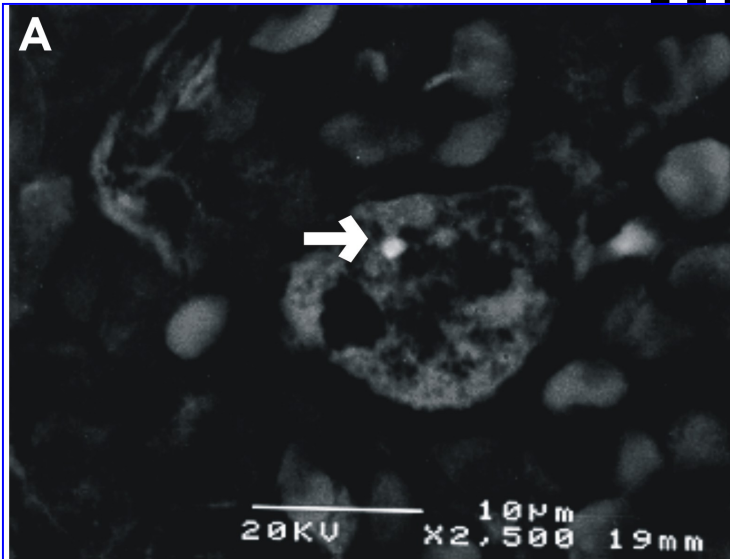
Tobacco Testing

- USAMRIID
 - Routine forensic testing
 - Ricin
- USDA
 - Bacteria (incl. Thermoactinomyces)
 - Fungi
- FDA
 - Toxins (strychnine, picrotoxinin, lobeline, diquat, paraquat)
 - Pesticide residues

Laboratory Investigation

- Sputum C/S for respiratory bacteria, fungus, virus
- Blood C/S aerobic and anaerobic
- Strep urine antigen
- Legionella pneumoniae urine antigen
- Legionella antibody
- Q fever antibody
- Mycoplasma pneumoniae antibody
- Adenovirus antibody
- Enterovirus antibody
- Influenza PCR and antibody
- SARS/Corona virus antibody
- Respiratory syncytial virus antibody
- RSV antigen
- Hantavirus panel
- Rickettsia antibody
- Antinuclear antibody screen
- Granulocyte antibody screen
- Pigeon fanciers disease panel
- Chlamydia pneumo and Chlamydia psittaci
- Stool check for intestinal ova/parasites
- Aspergillus
- Histoplasmosis
- Coccidioidomycosis

Scanning electron microscopy with EDX imaging



- Elemental composition of particles similar in both cases and controls
- Primarily pure silica and aluminum silica
- Presence of iron with sulfur in control lungs

Q-fever

- **Severe pneumonia cases reported in the literature***

Serology

Patient	Acute		Convalescent		Time
	IGM	IGG	IGM	IGG	
1	>1/1024	1/502	1/512	>1/1024	73
2			NEG	1/1024	102
3			NEG	>1/1024	133

* Q-fever Pneumonia Complicated by Acute Respiratory Distress Syndrome
Intensive Care Medicine (2001) 27

Acinetobacter Pneumonia

- Reported in healthy male employees of a steel-casting foundry exposed to unacceptably high levels of metallic dust and silica particles*
- *A. baumannii* is an unusually common cause of community-acquired pneumonia in the Northern Territory of Australia*